Regional Differences Invalidate U.S. Sperm Trend Conclusions

Regarding the continuing debate in *EHP* over the question of whether or not human sperm densities have declined in the United States, I feel compelled to respond to the statement by Swan et al. (*1*) that

> regional variation would not be inconsistent with the average decline that we demonstrated in Europe and the United States.

In referring to regional variation in sperm densities, Swan et al. cite the work of Fisch et al. (*2*) as indicating that sperm counts have not declined in the United States. In this study, sperm counts were analyzed in Los Angeles, California; Roseville, Minnesota; and New York, New York. A study by MacLeod and Wang (*3*) indicates that sperm counts have remained constant in New York since 1938. In addition, two other published studies report that sperm counts have not declined in Wisconsin (*4*) or in Seattle, Washington (*5*). There is not a single study of healthy men from any fertility center or sperm bank that has reported a decline in sperm counts in the United States.

The regional variation in sperm counts, with a nearly twofold difference in average sperm counts between Los Angeles and New York, invalidates any study that attempts to demonstrate a twofold decline in sperm counts based on trends over time in reporting of sperm counts from different regions of the United States (*6*). Despite the assertion of Swan et al. (*7*) that the data are robust, there can be no valid demonstration of a twofold decline in sperm counts in the United States when normal sperm counts vary nearly as much between Los Angeles and New York.

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On "Scents and Sensitivity"

I was delighted to learn of the informative article, "Scents and Sensitivity" [*EHP* 106:A594–A599 (1998)]. I would like to see this issue get the major media coverage it warrants.

Being extremely sensitive to fragrances, I have been seeking accommodation for over two years in the large office where I work. I was recently granted a private office space (without a door) and the firm purchased an air cleaner (HEPA with carbon pre-filter) for my use.

My employers' bottom line is that they are unwilling to request people to forego use of personal scented products in the office. I, however, am unwilling to wear a face mask all day in a work environment that would not, by nature of the work being done here, require anyone to wear a mask.

If a government agency were to publicly recognize that there is a health risk to some people from chemically based fragrances, offices such as the one where I work would be able to restrict use of scented personal products. The health of people such as myself would be greatly benefited and no one would be injured by the omission.

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Chlorpyrifos (Dursban) and Dow Employees

Papers published in *EHP* concerning adverse effects of pesticide exposure have helped protect the public's health. These include the study by Guillette et al. (*1*) concerning learning impairment in young children exposed to pesticides; the birth defects–pesticides study by Garry et al. (*2*); brain tumors in pesticide-exposed children (*3*); and the study by Gurunathan et al. (*4*) demonstrating volatilization and condensation of Dursban onto indoor surfaces, thus potentiating exposure.

The article by Gibson et al. (*5*) in the June issue of *EHP* raises a number of troubling questions. The authors failed to cite the reasons for EPA restrictions on the use of (chlorpyrifos) Dursban (*6,7*) and the EPA report that reviewed thousands of adverse reports to the EPA and poison control centers (*8*).

Gibson et al. (*5*) allege that chlorpyrifos is not mutagenic. Of the 28 Dursban toxicity tests reported in the EPA database for 1996, 19 were negative for gene mutation, 3 were positive for DNA damage, 1 was positive for aneuploidy, and 2 were positive for micronucleus disruption (*9*). Genetic damage was seen in applicators of pesticides (*10*).

Gibson et al. (*5*) claim that chloripyrifos is not teratogenic and does not adversely affect reproduction. In November 1996, under Section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), DowElanco itself reported 12 adverse reproductive effects to the EPA as a part of its late adverse reaction reports. A year later, Dow reported a thirteenth human case and adverse reproductive outcome in a breeder dog (*11*). The material safety data sheet for Dursban TC (*12*) states,

> Fetotoxicity and fetal development abnormalities were observed in a chronic ingestion study of pregnant mice, but the same dose produced severe maternal toxicity.

Chlorpyrifos, the pesticidal agent in Dursban, is both a chlorinated and organophosphate chemical, with toxicity characteristics of each class of chemicals. The product Dursban is a complex mixture, containing sulfotepp and trichloropyridinol (TCP) in addition to chlorpyrifos. TCP is used to manufacture chlorpyrifos, is found in the commercial product, is the metabolic breakdown product, and has been reported to be teratogenic at doses that are nontoxic to the mother (*13,14*).

Goldsmith et al. (*15*) reported birth defect cases in Israel. These pesticide exposures included Dursban, and were also reported directly to the U.S. EPA (*16*). Still Dow has been reluctant to accept the concept that exposure to a chlorinated organophosphate chemical designed to kill insects by interfering with neurological function could harm the developing human. Whitney et al. (*17*) reported specific cellular mechanisms for developmental neurotoxicity.

Gibson et al. (*5*) cited only four children with birth defects [see Sherman (*18*)]. There actually were eight children with birth defects who had been exposed *in utero* to Dursban (*19*). Discussing the findings, Gibson et al. (*5*) claimed lack of "consistency of symptoms among the children." Actually, the findings are not symptoms, but actual defects, and there is a strong pattern, calculated at odds of 10^{-45} for the first four children (*20*). Tabulation of eight children demonstrates a consistent pattern (see Table 1). In keeping with standard scientific methodology, other causes of birth defects have been explored (see Table 2).

Gibson et al. (*5*) state that I said "the mother's exposures to chlorpyrifos happened too late in the child's development

to be toxicologically significant." My statement was in response to a question from a judge in regard to another child that was not involved in the case under consideration (*21*). Although I expressed concern about testifying to facts in a case without the records before me and without the family being represented by their attorney, I was required to answer the judge's hypothetical questions. I testified (*19*) that the child's defects

> are the same pattern as the other seven children.... [A]nd he [the child] follows the same pattern of the boys in that all boys had undescended testicles.

When I reviewed the actual records, the record is clear: when the family home was treated with Dursban, the unborn son was an 11.5-week-old fetus. The child died at 7 years of age. His abnormalities, consistent with the reported pattern, were confirmed on autopsy. Thus, my testimony was not accurately represented by Gibson et al. (*5*). (Although I was paid to examine six of the children and to review the medical records of one child who subsequently died, I was not compensated for reviewing the documents for two of the children.)

To say that any mother's exposures to chlorpyrifos "happened too late in the child's development to be toxicologically significant" (*5*) would be inaccurate. Throughout intrauterine life, the developing fetus undergoes rapid cell growth, programmed cell death (apoptosis), and cell rearrangement, which are all time- and space-dependent. Interference with any of these processes results in abnormalities of subsequent growth and development. The specific disruption of intrauterine development depends upon both the inciting agent(s) and the state of development of the embryo, expressed subsequently as anatomic and/or functional defects. Thus, exposure later in fetal development or in infancy will result in defects that differ from those produced earlier in development. One child exposed to Dursban as an infant (*22*) became essentially quadriplegic (*21*). Wargo (*23*), the National Research Council (*24*), and the Food Quality Protection Act of 1996 agree on the special vulnerability of children to pesticide exposures.

Gibson et al. (*5*) further state that "Sherman's work does not adhere to general scientific standards used in medical and clinical practice." In the child's case cited by Gibson et al., I examined the child; interviewed the mother, father, and brother; visited the workplace where the mother's exposure occurred; visited the home of the child; spoke with the treating physician; read all of the child's and mother's medical records; and submitted over 10,000 pages of documents, which I rely on for my opinion. I have also published other teratology reports that link chemical exposure during pregnancy to birth defects (*25*).

Gibson et al. (*5*) cited the judge who ruled against the family of one of the Dursban-affected children as saying,

> My tentative view is that Dr. Sherman's case studies do nothing more scientifically than to suggest a causal relation.

Table 1. Birth defects in children exposed *in utero* to Dursban

	Child							
Defect	1	2	3	4	5	6	7	8
Sex of child	Female	Male	Male	Female	Female	Male	Female	Male
Brain defects								
Structural deformities	+	+	+	+	+	+	+	+
Ventricular	+	+	+	+	+	+	+	-
Microcephaly	+	+	+	-	+	+	-	-
Hydrocephaly	+	+	0	+	+	-	+	-
Atrophy of brain	-	+	+	-	+	+	+	-
Abnormality type	CC	CC	SP			DM	CC	CC
Eye defects								
Structural	Mi	Mi,C	Mi	CI			+	+
Blind	+	OT	+	0	+	LO	0	LO
Cataract	+	0	+	0	+	+	0	0
Facial								
Palate abnormality	+	+	+	+,Cp	+	+	+	+
Cleft lip	0	0	0	+	0	0	CT	+
Tooth abnormality	+	0	+	+	+	-	+	+
Nose abnormality	+	0	0	+	SM	SM	+	+
External ear	+	+	0	+D	0	0	+	+
Other	7N	AS	AS					RP
Heart	-	H1	H2	-	U	+	-	AS,D
Genital								
Abnormal external	+	+	+	0	+	+	U	+
Specific abnormality	F	U	U,P			U,P		U,P
Other								
Mental retardation	+	+	+	N	+	+	+	+
Nipples wide-spread	+	0	+	+	+	+	+	+
Foot abnormalities	+	+	+	0			+	-
Hypotonia	+	+	+	-		+	+	+
Growth retardation	+	+	+	+	+	+	-	+

Abbreviations: N, normal; 0, defect not present; +, defect present; Cp, cleft palate; CC, corpus callosum; SP, septum pellicudum; Mi, micro-ophthalmia; C, cyst of eye; CI, cleft in eye; OT, optic tracts abnormal; D, totally deaf; F, fused labia; U, undescended testes; P, microphallus; DM, demyelinization; CT, cleft tongue; 7N, seventh cranial nerve palsy; AS, asymmetry; H1, atrial–septal defect and pulmonary stenosis; H2, right aortic arc; LO, low vision; SM, unusually small nose; RP, paralysis on right side of face; -, defect not apparent, determination delayed until growth is achieved, and/or surgical and autopsy findings.

Table 2. Review of medical history and chemical exposures

	Child							
Findings	1	2	3	4	5	6	7	8
Chromosome studies	N	N	N	N	N	N	N	N
Maternal smoking	No	No	No	No	No	No	No	No
Maternal alcohol use	No	No	No	A	No	No	No	No
Infections during pregnancy	No	PU	No	No	No	No	No	No
Pregnancy medication use	T	S	T	0	Ty	Ty	Pr	0
Family history of birth defects								
Child's mother	0	0	0	0	0	0	0,CB	0
Child's father	0	0	0	0	0	0	0,LD	0
Mat grandmother	0	0	0	0	0	0	0	0
Mat grandfather	U	0	U	0	0	0	0	0
Pat grandmother	0	0	0	0	0	0	0	0
Pat grandmother	0	0	0	0	0	0	0	0
Birth defects in other siblings	0	0	0	0	0	0	0	0
Other chemical exposures during pregnancy	0	C	0	F	0	0	Cy	D/B
Dursban product used	LO	TC	LO	LO	PU	PU	270	Sp

Abbreviations: Mat, maternal; Pat, paternal; N, normal; 0, none; A, "a couple of sips of wine one time during pregnancy"; T, occasional Tylenol; S, occasional Sudafed, amoxicillin (1 course of treatment); C, home previously treated with chlordane ; F, firefog; U, unknown; Cy, cypermethrin; CB, craniostosis in brother's child; LD, learning disability in seizure in past; Ty, "maybe a Tylenol"; Pr, progesterone; Sp, Spectricide; D/B, diazinon/Bengal spray; PU, specific Dursban product is unknown; LO, TC, PU, 270, and Sp are specific Dursban products.

That there is a causal relationship, based upon human case finding, animal testing, biochemistry, and structure–activity relationships, is precisely the point. This has also been demonstrated by additional independent physicians and scientists and appears in various publications and court records.

The cost of caring for one of these totally dependent children is in excess of $500,000. The financial, emotional, social, and physical burdens upon the families is staggering. Prevention is imperative.

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Response to Sherman

We find it unnecessary to address all statements made by Janette Sherman in her letter about our article in the June issue of *EHP* (*1*). It is important to note that the Centers for Disease Control and Prevention (CDC), the U.S. EPA, and the California EPA have each reviewed Sherman's arguments and purported evidence and concluded that Sherman has failed to establish a legitimate association between human exposure to chlorpyrifos and teratogenicity. In a letter to Jerome Blondell of the U.S. EPA (*2*), the CDC commented on Sherman's evidence as follows:

> At the present, there does not appear to be a consistent phenotypic pattern of anomalies among the infants whose records we reviewed. In addition, you reported that [chlorpyrifos] is used extensively in the United States. Based on the available medical records and the likely high frequency of this exposure, we would be hesitant to recommend pursuing major epidemiological studies at this point in time.

Subsequently, on 14 January 1997, Blondell issued a memorandum (*3*) which stated that

> HED [the Health Effects Division of the EPA] concludes that available evidence does not support a finding of teratogenicity based on human epidemiology studies and case reports.

Similarly, in a memorandum dated 27 January 1997 (*4*), R. Cochran, staff toxicologist of the Medical Toxicology Branch of the Department of Pesticide Regulation of the California EPA stated

> There was no scientific evidence presented in either paper by Dr. Sherman which supported the contention that chlorpyrifos could cause birth defects—either in laboratory animals or humans.

In addition to government scientists and regulators, two independent panels of scientific experts have comprehensively reviewed published chlorpyrifos toxicology and epidemiology studies, including Sherman's papers, and both have rejected the scientific validity of any claims associating chlorpyrifos exposure with birth defects (*5,6*).

We stand behind our paper in all respects, and we feel that any objective review of the relevant data will strongly support our conclusions.

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